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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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 SAN DIEGO, CA 92130

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

04 NOV 2005

FOR FURTHER ACTION

See paragraph 2 below

Applicant's or agent's file reference

45026.141.WO

International application No.

International filing date (day/month/year)

PCT/US04/23788

16 July 2004 (16.07.2004)

Priority date (day/month/year)

16 July 2003 (16.07.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C 07C 69/76, 61/00, 51/16 and US Cl.: 560/008; 562/400, 405

Applicant

LIGAND PHARMACEUTICALS INCORPORATED

1. This opinion contains indications relating to the following items:

Box No. I Basis of the opinion

Box No. II Priority

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Box No. IV Lack of unity of invention

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Box No. VI Certain documents cited

Box No. VII Certain defects in the international application

Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

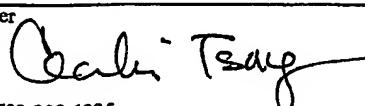
3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
 Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 Facsimile No. (703) 305-3230

Authorized officer

Cecilia Tsang

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

a sequence listing
 table(s) related to the sequence listing

b. format of material

in written format
 in computer readable form

c. time of filing/furnishing

contained in international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.

3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application
 claims Nos. 43

because:

the said international application, or the said claim Nos. 43 relate to the following subject matter which does not require an international preliminary examination (specify):

Claim 43 recites "Error! Reference source found.." Apparently the intended claim was deleted. Technically, the said phrase is directed to a nonstatutory subject matter.

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (specify):

the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. _____

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished
 does not comply with the standard
 has not been furnished
 does not comply with the standard

the computer readable form

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
 - paid additional fees
 - paid additional fees under protest
 - not paid additional fees
2. This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
 - complied with
 - not complied with for the following reasons:

See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

all parts.

the parts relating to claims Nos. 1-42 in part and claims 44-64 in part, wherein variable Group X is methylene, variable group Y is oxygen and none of the other variable moieties are heterocyclic units. Please note that claims 13, 20, 34, 41, 56 and 63 are not embraced in the elected group because in the said claims variable Y is defined as a methylene group. Thus, the said claims are excluded from the instant Examination.

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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO
Inventive step (IS)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO
Industrial applicability (IA)	Claims <u>Please See Continuation Sheet</u>	YES
	Claims <u>Please See Continuation Sheet</u>	NO

2. Citations and explanations:

Claims 1 in part, 3 in part, 22 in part, 24 in part, 44 in part and 46 in part lack novelty under PCT Article 33(2) as being anticipated by CA 2002:487541 for Beswick et al. Beswick discloses HPPAR delta agonist claimed to be useful in the treatment of diabetes, hyperlipidemia, obesity cardiovascular disease and other medical conditions. Among the compounds disclose by Beswick is 3-methyl-4-(phenylmethoxy)-benzaldehyde having a registry number 158771-31-4.

Claims 1 in part, 3 in part, 22 in part, 24 in part, 44 in part and 46 in part lack novelty under PCT Article 33(2) as being anticipated by CA 2002:964313 for Brooks et al. Brooks discloses PPAR agonist and co agonist claimed to be useful in the treatment of diabetes, hyperlipidemia, obesity cardiovascular disease and other medical conditions. Among the compounds disclose by Brooks is 4-(phenylmethoxy)-3-(trifluoromethyl)-benzaldehyde having a registry number 477980-90-8.

Claims 1 in part, 3 in part, 10-11 in part, 14-19 in part, 22 in part, 24 in part, 44 in part, 46 in part, 53-54 in part and 57-62 in part lack novelty under PCT Article 33(2) as being anticipated by Tajima et al, WO 9911255 (1999).

Tajima discloses HPPAR delta agonist claimed to be useful in the treatment of diabetes, hyperlipidemia, obesity cardiovascular disease and other medical conditions. Among the compounds disclose by Tajima et al are:

4-(1-naphthalenylmethoxy)-benzeneacetic acid, having a registry number 125721-57-5

4-(2-naphthalenylmethoxy)-benzoic acid, having a registry number 148066-83-5

4-(2-naphthalenylmethoxy)-benzene propanoic acid, having a registry number 221261-24-1

4-(2-naphthalenylmethoxy)-benzene butanoic acid, having a registry number 221261-99-0 and

4-(2-naphthalenylmethoxy)-benzeneacetic acid, having a registry number 221265-57-2.

Claims 1-12 in part, 14-19 in part, 21-33 in part, 35-40 in part, 42 in part, 44-55 in part, 57-62 in part, and 64 in part meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V.1. Reasoned Statements:

The opinion as to Novelty was positive (Yes) with respect to claims 2 in part, 4-9 in part, 12 in part, 21 in part, 23 in part, 25-30 in part, 33 in part, 42 in part, 45 in part, 47-52 in part, 55 in part, 64 in part.

The opinion as to Novelty was negative (No) with respect to claims 1 in part, 3 in part, 10-11 in part, 14-19 in part, 22 in part, 24 in part, 31-32 in part, 35-40 in part, 44 in part, 46 in part 53-54 in part, 57-62 in part.

The opinion as to Inventive Step was positive (Yes) with respect to claims 2 in part, 4-9 in part, 12 in part, 21 in part, 23 in part, 25-30 in part, 33 in part, 42 in part, 45 in part, 47-52 in part, 55 in part, 64 in part.

The opinion as to Inventive Step was negative (No) with respect to claims 1 in part, 3 in part, 10-11 in part, 14-19 in part, 22 in part, 24 in part, 31-32 in part, 35-40 in part, 44 in part, 46 in part, 53-54 in part, 57-62 in part.

The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-12 in part, 14-19 in part, 21-33 in part, 35-40 in part, 42 in part, 44-55 in part, 57-62 in part and 64 in part.

The opinion as to Industrial Applicability was negative (NO) with respect to claims NONE